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Protocol of a prospective, monocentric phase I/II feasibility study investigating the safety of multimodality treatment with a *combi*nation of intraoperative *C*hemotherapy *a*nd surgical *Re*section in locally confined or borderline resectable pancreatic cancer: The combiCaRe study

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ABSTRACT

Introduction

Pancreatic cancer is a devastating disease with an exceptionally poor prognosis. Complete resection of the primary tumour followed by adjuvant chemotherapy is the current standard treatment for patients with resectable disease and the only curative treatment option. However, long-term survival remains rare. Tumour cell dissemination due to manipulation during surgery may increase the rate of future metastases and local recurrence, and perioperative chemotherapy might diminish local, distant and circulating minimal residual disease. Yet, safety and feasibility of systemic chemotherapeutic treatments during pancreatic cancer resection have to be evaluated in a first instance.

Methods and analysis

This is a prospective, single-centre phase I/II feasibility study to investigate the safety and tolerability of a combination of intraoperative chemotherapy and surgical resection in pancreatic cancer. Forty patients with locally confined or borderline resectable pancreatic cancer, meeting all proposed criteria will be included. Participants will receive 400 mg/m^2 leucovorin over 2 hours and 2000 mg/m^2 5-fluorouracil (5-FU) over 48 hours, started on the day before pancreatic surgery and thus continuing during surgery. Participants will be followed until 60 days after surgery. The primary endpoint is the 30-day overall complication rate according to the Clavien-Dindo classification. Secondary endpoints comprise toxicity and treatment associated complications. Patients receiving perioperative chemotherapy will be compared to a propensity score matched contemporary control group of 70 pancreatic cancer patients receiving the standard treatment. This trial also contains an ancillary translational study to analyse disseminated tumour cells and effects of pharmacologic

interventions in pancreatic cancer.

Ethics and dissemination

CombiCaRe has been approved by the German Federal Institute for Drugs and Medical Devices (reference number 4042787) and the Medical Ethics Committee of Heidelberg University (reference number AFmo-269/2018). The results of this trial will be presented at national and international conferences and published in peer-reviewed journals.

Trial registration number

DRKS00015766

Strengths and limitations of this study

- This is the first prospective clinical safety and feasibility study to evaluate a novel concept of systemic intraoperative chemotherapy during pancreatic cancer surgery.
- A strength of this study is the careful monitoring of any potential toxicity and treatment related complications, and the comparison of the safety profile of this multimodal therapy compared to the standard treatment by inclusion of a propensity score matched contemporary control group.
- If intraoperative chemotherapy during pancreatic cancer surgery proves to be safe, the data will be used as a baseline for a randomised controlled, phase III trial on the oncological effectiveness of this treatment.
- This study will provide valuable information for a better understanding of tumour cell dissemination and effects of pharmacological interventions in pancreatic cancer.

INTRODUCTION

Pancreatic cancer is the 4th leading cause of cancer-related deaths in the Western world, and it is one of only a few cancers for which mortality has increased since 1990[1]. In addition, mortality is projected to further increase, making this devastating disease the 2nd leading cause of cancer related death within the upcoming decade. With a 5-year survival rate of about 7%[2 3] the prognosis of pancreatic cancer is still very poor.

Surgical resection is the only curative treatment option and primary surgery followed by adjuvant chemotherapy is the current standard treatment for patients with resectable pancreatic cancer[4-7]. Local resectability of pancreatic cancer is determined by the

involvement of adjacent major vessels and neighboring organs. An international consensus on the classification of resectability, especially of borderline resectable pancreatic cancer, has recently been developed by the International Study Group of Pancreatic Surgery (ISGPS)[8] and the International Association of Pancreatology[9]. However, only a minority of patients are diagnosed with resectable disease and even after potentially curative R0 resection the 5-year survival rate remains 15-30%[10-14]. The cornerstone of tumour resection in pancreatic cancer treatment has been further corroborated by a National Cancer Data Base study in the US, which showed that the 5-year survival rate of patients with resectable pancreatic cancer drops below 3% if surgery is omitted[13]. Following resection, adjuvant chemotherapy offers a survival benefit for pancreatic cancer patients, and numerous multicentre randomised trials performed over the past two decades showed considerable advances of chemotherapeutic regimens in the adjuvant setting[14-26]. Additional progress has been made in increasing the resection rate of locally advanced unresectable pancreatic cancer by neoadjuvant chemotherapy, especially combinations of leucovorin, 5-fluorouracil (5-FU), irinotecan and oxaliplatin (FOLFIRINOX)[27], associated with improved overall survival and potential cure. Neoadjuvant chemo(radio)therapy might also be beneficial in patients with resectable or borderline resectable pancreatic cancer[28-30].

Besides improvements in chemotherapeutic regimens, the safety of pancreatic surgery has considerably increased, with a reduction of postoperative mortality to 3%[12], which is mainly due to advances in complication management, especially at high-volume pancreatic surgery centres[12 31-33]. The most common and serious complication following pancreatic surgery is a leakage of pancreatic juice containing digestive enzymes out of the remnant pancreas, a so-called postoperative pancreatic fistula (POPF)[34 35]. The aggressive nature of the leaking

pancreatic juice might cause life-threatening complications, including postpancreatectomy hemorrhage (PPH), or intraabdominal fluid-collection with superinfection leading to abscess formation and sepsis. These complications, together with delayed gastric emptying (DGE) and chyle leak following pancreatic surgery, have been comprehensively defined by the ISGPS with associated severity gradings[34-38]. Postoperative complications might delay adjuvant treatments or compromise their completeness, associated with diminished effectivity and increased risk of recurrent disease.

Despite advances in surgery and (neo-)adjuvant chemotherapy long-term survival of pancreatic cancer patients is still rare, due to frequent local or systemic recurrence[39-41], while the pathophysiology of recurrence remains largely unknown. Subclinical metastasis might occur early during tumour development[42 43], but iatrogenic tumor cell dissemination as a result of tumour manipulation during surgery is also a relevant concern[44 45]. There is evidence that cancer cells are continuously released from the primary tumour into the bloodstream and lymphatic system, and circulating tumour cells (CTCs) are further increased by standard pancreaticoduodenectomy[45]. Since surgical manipulation of the tumour during pancreatic resection leads to dissemination of pancreatic cancer cells potentially founding the seeds for future metastases and local recurrence, perioperative systemic chemotherapy may reduce recurrence and thereby increase long-term survival by targeting intraoperatively shed cells as well as pre-existing micrometastases. So far, for pancreatic cancer no systemic intraoperative chemotherapeutic regimen has been studied in a standardized prospective manner to potentially reduce local and distant recurrences by targeting minimal residual disease such as CTCs. There is limited evidence available demonstrating hyperthermic intraperitoneal chemotherapy (HIPEC) with gemcitabine after R0 pancreatic cancer resection

leads to a survival benefit by controlling locoregional recurrence without increasing perioperative morbidity and mortality[46]. Cytoreductive surgery including multiorgan resection combined with HIPEC is a well-established treatment option for peritoneal carcinomatosis of several gastrointestinal tumour entities, and the operative risk of the procedure has been shown to be similar to any other major gastrointestinal surgery[47 48] indicating that intraoperative systemic chemotherapy during pancreatic resections should be well tolerated.

Thus a multimodal treatment concept with a *combi*nation of intraoperative *C*hemotherapy *a*nd surgical *Re*section in patients with locally confined or borderline resectable pancreatic cancer (combiCaRe study) has been developed. Based on the above mentioned rationale it has been hypothesised that the number of CTCs can be reduced by this approach. This might translate into a longer interval from pancreatic cancer resection to tumour recurrence and extended overall survival. Because intraoperative chemotherapy for pancreatic cancer has not been tested in a standardized prospective trial, the feasibility and safety of this approach will be evaluated within this prospective, monocentric phase I/II study. In addition, translational aspects of tumour cell dissemination as well as effects of chemotherapy in pancreatic cancer tissue and blood will be determined. As a proof of concept the combiCaRe study aims to define the basis for a consecutive confirmatory phase III clinical trial investigating the oncologic benefit of this multimodal treatment.

METHODS AND ANALYSIS

Study design

The combiCaRe trial is a prospective, monocentric phase I/II clinical study, conducted at the

high-volume pancreatic surgery centre of Heidelberg University Hospital (Germany) to determine the feasibilty and safety of a combination of intraoperative chemotherapy and surgical resection in locally confined or borderline resectable pancreatic cancer. This study was registered at the German Clinical Trials Register (DRKS00015766). The study protocol adheres to the SPIRIT recommendations (Standard Protocol Items: Recommendations for Interventional Trials)[49].

After screening for eligibility, written informed consent, and enrolment to the trial, chemotherapy with 5-FU and leucovorin will be started the day prior to surgery. Thereby adequate levels of cytotoxic substances will be reached within the systemic circulation during the critical period of tumour manipulation and potential intraoperative tumor cell dissemination. Pancreatic cancer surgery will be performed according to the standards of care in the Department of Surgery at Heidelberg University Hospital. Administration of chemotherapy will be continued for 48 hours in total. Postoperative care will be provided according to regular standards with particular attention to chemotherapy associated side effects. Adjuvant treatment regimens are performed according to current guidelines, starting up to 12 weeks after surgery. The study flow chart is presented in figure 1.

Study population and eligibility criteria

Patients with newly diagnosed resectable, or borderline resectable pancreatic cancer as defined by the ISGPS[8], located in the head of the pancreas, scheduled for elective primary pancreatic cancer resection will be approached for participation in this study. All patients will be informed in detail about the purpose of the trial, the surgical procedure, the perioperative

chemotherapeutic treatment and potential benefits as well as risks. If the patient has given written informed consent to participate in the trial, inclusion and exclusion criteria (Box 1) will be carefully evaluated. Eligible patients will be enrolled into the trial. Screened patients who are not enrolled will be documented in the screening log, including the reasons for exclusion.

Box 1. Major inclusion and exclusion criteria of the trial

Inclusion criteria

- newly diagnosed, resectable or borderline resectable pancreatic cancer located in the head of the pancreas, without arterial involvement on cross sectional imaging (contrast enhanced CT scan) according to the International Study Group of Pancreatic Surgery (ISGPS) criteria[8]
- histologically or cytologically proven pancreatic ductal adenocarcinoma (including variants)
- ≥ 18 and ≤ 75 years of age
- capacity to consent
- written informed consent
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- patient considered to tolerate surgery and chemotherapy by a multidisciplinary team
- Women of childbearing potential and men must agree to use adequate contraception prior to study entry and for the duration of study participation. Childbearing potential is defined according to the “Recommendations related to contraception and pregnancy testing in clinical trials“ of the Clinical Trial Facilitation Group (CTFG).

Exclusion criteria

- distant metastatic disease
- renal disease, creatinine clearance < 50 ml/min (estimated by Cockroft-Gault)
- abnormal hepatic function as defined by a total bilirubin level > 1.5 x the upper limit of normal (ULN), unless the patient has extrahepatic cholestasis due to pancreatic cancer, or alanine aminotransferase (ALT) > 2.5 x ULN, liver cirrhosis (of any Child-Pugh grade)
- serious cardiovascular disease (e.g. myocardial infarction in the last 12 months, congestive heart failure NYHA III/IV, unstable angina pectoris)
- severe chronic obstructive pulmonary disease (COPD), GOLD stage > II
- American Society of Anesthesiologists (ASA) score > III
- active infection, including cholangitis
- abnormal bone marrow function, defined as an absolute white blood cell count < 3/nl or platelet count < 100/nl
- pernicious anaemia or other megaloblastic anaemias where Vitamin B12 is deficient
- immunosuppressive therapy
- allergy or known intolerance to 5-fluorouracil (5-FU) or leucovorin
- patients with a known lack of dihydropyrimidine-dehydrogenase (DPD)-activity or patients treated with DPD inhibitors such as brivudine
- current pregnancy or breastfeeding; each pregnancy that occurs within 6 months after the termination of the perioperative chemotherapy has to be reported
- history of another malignancy in the past 5 years
- inability to comply with the study and/or follow-up procedures
- (language) problems in understanding the patient information document explaining the present clinical trial

- concurrent participation in another clinical study
- any condition, which could result in an undue risk for the patient in the opinion of the investigator

Subject withdrawal

Subjects may withdraw their consent at any time, without stating the reason and without any disadvantage. Patients may also be excluded for other reasons, if the investigator assesses a continuation of the treatment as detrimental to the subject's well-being.

Sample size

This exploratory study focuses on the feasibility and safety of the therapeutic interventions. No formal sample size calculation has been performed. Therefore, we have chosen a number of patients, which is estimated to be sufficient to obtain first data on feasibility and safety of the intervention. Forty patients are planned to be enrolled in this trial, including 5 patients who potentially drop out intraoperatively, e.g. due to liver or peritoneal metastasis revealed by exploratory laparotomy. To compare the outcomes of the intervention group with a similar control group, the enrolled patients will be matched by propensity score with a contemporary cohort (age, procedures, histopathological findings, and medical history) extracted from the pancreatic surgery databases of the Department of Surgery at Heidelberg University Hospital in a 1:2 ratio. This sample size (35:70) would be large enough to detect a standardized mean difference (Cohen's d) of about 0.6 with 80% power and a significance level of 5%. A subsequent randomised controlled trial is planned with further sample size

calculation based on the results of this trial and all other available data.

Study procedures

Perioperative chemotherapy

Chemotherapy with 5-FU is started 12-18 hours prior to surgery and continued until postoperative day 1. Thereby adequate systemic levels of cytotoxic substances will be reached during the critical period of tumour manipulation and potential intraoperative tumour cell dissemination. Overall, 1000 mg/m^2 5-FU per day are applied for 48 hours (total dose 2000 mg/m^2). The 5-FU infusion is administered via peripheral vein catheter. Immediately prior to 5-FU, 400 mg/m^2 leucovorin will be given intravenously over 2 hours.

Surgery, biospecimen and data collection

(Partial) pancreaticoduodenectomy will be performed according to the standards of care in the Department of Surgery at Heidelberg University Hospital. Peripheral blood will be collected prior to the start of chemotherapy, as well as on postoperative days 3, 7, 14 (or day of discharge) and 30. Intraoperatively, peripheral and portal venous blood, bone marrow and tumour tissue dispensable for pathological diagnosis and staging will be collected for translational studies. The department's well-established and highly standardized local biobanks will be the backbone of this study. Perioperative management and postoperative care will be provided according to regular standards with particular attention to chemotherapy-associated side effects. In addition, on postoperative days 3, 7, 14 (or the day of discharge) qualified study personnel will visit the patient for the assessment of the study

endpoints and to take peripheral blood. Thirty days after surgery patients will be examined in the department's outpatient clinic for the occurrence of any further surgery- or chemotherapy-related complications. Sixty days after surgery patients will be contacted by telephone and asked for the occurrence of any further intervention-related complications. Adjuvant treatment regimens are performed according to current guidelines and in accordance with the recommendations of the National Centre of Tumour Disease (NCT) of Heidelberg University Hospital, starting up to 12 weeks after surgery. Patients are followed until postoperative day 60.

Study endpoints

Primary study endpoint

The primary objective of this study is to determine the safety of a perioperative chemotherapeutic regimen in combination with pancreatic cancer resection, which will be measured by the overall 30-day complication rate according to the Clavien-Dindo classification[50]. In parallel, the feasibility of this novel treatment concept will be assessed by the completeness of perioperative chemotherapy administration in relation to its toxicity, timely patient recruitment, and proper collection of biospecimen.

Secondary study endpoints

Key secondary outcomes include:

- 60-day complication rate according to the Clavien-Dindo classification[50]
- 30- and 60-day mortality

- pancreas-associated postoperative morbidity: POPF, PPH, DGE, and chyle leak (according to the ISGPS definitions[34-38]), intraabdominal fluid-collection or abscess
- bile leakage, including insufficiency of the biliodigestive anastomosis
- perioperative bleeding
- gastrointestinal bleeding
- postoperative ileus
- duration of intensive care unit (ICU) stay (postoperative and readmissions)
- postoperative duration of hospital stay
- need for readmission
- anaemia (Hb < 8 g/dl), thrombocytopenia, leukopenia
- postoperative sepsis
- allergic reactions
- serotonin syndrome
- mucositis (stomatitis, cheilitis, esophagitis, proctitis), diarrhea, nausea, vomiting
- alopecia, hand-and-foot syndrome
- central neurotoxicity, peripheral neuropathy
- renal failure (serum creatinine, BUN, urine production)
- liver damage (AST > 5 x ULN, ALT > 5 x ULN, AP > 5 x ULN, GGT, bilirubin > 1.5 x ULN)
- cardiotoxicity
- bronchospasm
- perioperative tumour cell dissemination (circulating tumor cells, CTCs)
- pharmacokinetics of perioperative chemotherapy

Safety objectives and assessment of safety

The incidence of all adverse events (AEs) will be closely monitored and evaluated. Hereby, only events that occur after the study inclusion and during the follow-up period will be collected. All AEs and intervention related side effects will be documented on the specific forms and will be reported regardless of causality. In addition, each serious adverse event (SAE) has to be documented on a SAE form and transmitted to the pharmacovigilance department within 24 hours after investigator's awareness of its occurrence. Following treatment of the first 10 patients recruitment will be interrupted for at least 30 days until an interim analysis for safety has been performed. If one of the following specific stopping criteria will be reached, the combiCaRe trial will be stopped immediately: grade B or C POPF[34 35] in more than 5 patients; insufficiency of the biliodigestive anastomosis in more than 4 patients; death within 30 days in more than 2 patients.

Ancillary translational study

CTCs will be quantified, molecularly and functionally analysed in the systemic circulation and portal venous blood before, during and after pancreatic cancer resection. In addition, disseminated tumor cells (DTCs) in the bone marrow will be assessed via bone marrow biopsy during surgery. The effects of perioperative chemotherapy on CTC and DTC biology will be determined. The biodistribution of 5-FU within pancreatic cancer tissue following perioperative 5-FU administration and oncologic resection will be analysed and potential immediate effects of pharmacologic interventions on tumour cell survival will be monitored in resected pancreatic cancer tissue. Comprehensive histopathological and molecular analyses

will be performed for in depths characterisation of immediate immune responses to chemotherapy-induced cell death in pancreatic cancer. Further functional assays using organ culture systems will help to determine the effect of 5-FU treatment on stroma - tumor cell crosstalk within an intact tumour microenvironment, and provide a valuable *in vitro* tool for screening drugs with potential synergistic antitumour activity. This might help to design more efficient, personalised (immuno)therapies against pancreatic cancer.

Data handling and monitoring

All protocol-required information collected during the trial must be entered by the investigator, or designated representative, into the electronic case report form (eCRF). The completed eCRF must be reviewed and authorised electronically by the investigator or by a designated co-investigator. To guarantee high data quality, data validation rules will be defined in a data validation plan. Completeness, validity and plausibility of data will be checked using validating programs, which will generate queries. A tracking system for eCRF data and queries will be established to guarantee that data is managed in a timely manner. All data management procedures will be conducted according to written defined standard operating procedures (SOPs) of the Institute of Medical Biometry and Informatics (IMBI) at Heidelberg University Hospital that guarantee an efficient conduct complying with Good Clinical Practice (GCP). To ensure confidentiality of patients' personal information data will be stored, and analysed in a pseudonymised manner and protected against unauthorised access. Only participating investigators or designated representatives will have the authority to access the data. Monitoring will be conducted by the Coordination Centre for Clinical Trials (KKS) Heidelberg. The monitor ensures that the trial is conducted according to study protocol and

regulatory requirements by review of source documents, entries into the eCRF and essential documents.

Statistical analysis

The empirical distribution of all endpoints will be calculated, including mean, standard deviation and quartiles in case of continuous variables and scores, and with absolute and relative frequencies in case of categorical data. Two-sided 95% confidence intervals will be calculated. Descriptive p-values of the corresponding statistical tests comparing the two samples (intraoperative chemotherapy and surgical resection vs. surgical resection alone from historical control) will be reported. Whenever appropriate, statistical graphics will be used to visualize the findings. Besides an intention-to-treat (ITT) analysis, a modified ITT analysis will be performed to separately analyse patients receiving partial pancreaticoduodenectomy including a pancreatico-digestive anastomosis.

Ethics

The trial will be carried out in conformity with the “Ethical principles for medical research involving human subjects” of the 18th World Medical Association General Assembly in Helsinki (1964), including all amendments. The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) harmonised tripartite guideline on Good Clinical Practice (ICH-GCP) and the ethical principles described in the

applicable version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements. The protocol of the combiCaRe trial (version 02, date July 27th 2018) was approved by the German Federal Institute for Drugs and Medical Devices (reference number 4042787) on August 20th 2018 and reviewed by the Medical Ethics Committee of Heidelberg University that provided a favourable opinion (reference number AFmo-269/2018) on September 11th 2018. Thus, all measures have been taken to guarantee patient welfare and minimise ethical concerns. Any subsequent protocol amendments must be evaluated by the ethics committee and competent authority.

As described above, systemic chemotherapy during HIPEC is an established treatment regimen in colorectal cancer or other malignancies spread to the peritoneal cavity. 5-FU based regimens have been shown to be effective in (neo)adjuvant and palliative pancreatic cancer therapy. Therefore, the perioperative application of 5-FU can be performed during a standard pancreatic cancer resection without expected SAEs. General complications of both, the chemotherapeutic regimen and surgical procedures, are subject of patients' informed and written consent. The occurrence of all treatment-emergent adverse events (TEAEs), AEs, SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be rigorously monitored. Immediate intervention or treatment is available in case of an acute AE.

Before being enrolled in the study, the subject is informed about the nature, scope and possible consequences of the study in a way understandable to the patient. An informed consent document that includes both information about the study (including ancillary translational study) and the consent form is prepared and given to the subject in a language understandable to the patient. After reading the informed consent document, the subject

must give written informed consent to participate in the study. A copy of the signed consent document is given to the subject and the original document is retained by the investigator. Without the patient's written informed consent, any measures or procedures required only for the clinical study are not permitted.

Patient and public involvement

Although patients or public were not involved in the design of the present study, our first priority was the patients' well-being. Patients will be informed about novel insights with regard to this clinical trial that might be relevant to their participation in this study. At any time, participants can be informed about study outcomes through the principal investigator. Furthermore, the results of this study are planned be presented at meetings of self-supporting groups for patients with pancreatic diseases and their relatives and friends, e.g. the "Arbeitskreis der Pankreatektomierten e.V.".

Dissemination

The results of this trial will be presented at relevant national and international conferences and will be published in peer-reviewed journals, regardless of the outcome of this study. After analysis of the primary endpoint a first manuscript reporting study results is planned to be published as soon as possible. All presentations and manuscripts will be reviewed by the principal investigator to prevent forfeiture of patient rights to data not in the public domain.

Author contributions

All authors contributed to the design of the study protocol and approved the final manuscript.

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Disclaimer

The sponsor and funders have no role in the study design, data collection and analysis, nor in publication of study results.

Competing interests statement

None declared.

Trial status

Recruitment planned.

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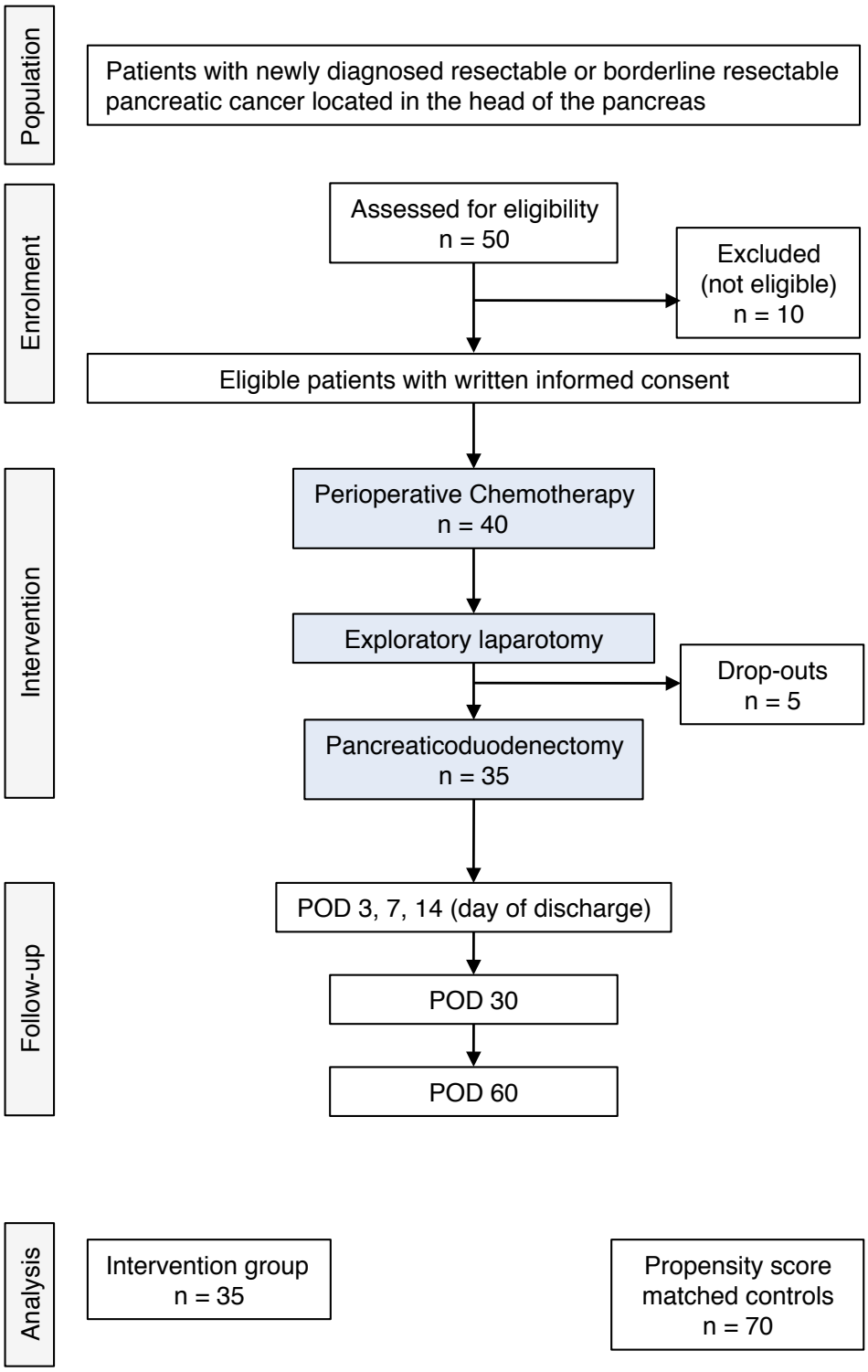
FIGURE LEGENDS

Figure 1. Study flow chart. CTx: Chemotherapy with 5-fluorouracil (5-FU) and leucovorin; pod: postoperative day.


Population
Patients with newly diagnosed resectable or borderline resectable pancreatic cancer located in the head of the pancreas
Enrolment
Assessed for eligibility
n = 50
Excluded
(not eligible)
n = 10
Eligible patients with written informed consent
Intervention
Perioperative Chemotherapy
n = 40
Exploratory laparotomy
Drop-outs
n = 5
Pancreaticoduodenectomy
n = 35
Follow-up
POD 3, 7, 14 (day of discharge)
POD 30
POD 60
Analysis
Intervention group
n = 35
Propensity score
matched controls
n = 70

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/ item	Item No	Description	Manuscript page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**2**
	2b	All items from the World Health Organization Trial Registration Data Set	**see DRKS registry**
Protocol version	3	Date and version identifier	**12**
Funding	4	Sources and types of financial, material, and other support	**14**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**1, 14**
	5b	Name and contact information for the trial sponsor	**14**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**14**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**Not applicable**
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**3-5**
	6b	Explanation for choice of comparators	**8**
Objectives	7	Specific objectives or hypotheses	**9-10**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**5-6**
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**5**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**6-7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**8**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**7, 10**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**Not applicable**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**Not applicable**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**9-10**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**Figure 1**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**8**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**Not applicable**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**Not applicable**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**Not applicable**

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**Not applicable**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**Not applicable**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**Not applicable**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**8-9**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**Not applicable**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**11**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**11-12**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**11-12**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**11-12**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**11**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**10**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**10**

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**Not applicable**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**12**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**12**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**12-13**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**12-13**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**11**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**14**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**11**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**Not applicable**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**13**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**Not applicable**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**Not applicable**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**Available at request**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**Available at request**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Protocol of a prospective, monocentric phase I/II feasibility study investigating the safety of multimodality treatment with a combination of intraoperative Chemotherapy and surgical Resection in locally confined or borderline resectable pancreatic cancer: The combiCaRe study

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Surgery, Oncology
Keywords:	Pancreatic disease < GASTROENTEROLOGY, Gastroenterology < INTERNAL MEDICINE, Gastrointestinal tumours < ONCOLOGY, Pancreatic surgery < SURGERY

Protocol of a prospective, monocentric phase I/II feasibility study investigating the safety of multimodality treatment with a *combi*nation of intraoperative *C*hemotherapy *a*nd surgical *Re*section in locally confined or borderline resectable pancreatic cancer: The combiCaRe study

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ABSTRACT

Introduction

Pancreatic cancer is a devastating disease with an exceptionally poor prognosis. Complete resection of the primary tumour followed by adjuvant chemotherapy is the current standard treatment for patients with resectable disease and the only curative treatment option. However, long-term survival remains rare. Tumour cell dissemination due to manipulation during surgery may increase the rate of future metastases and local recurrence, and perioperative chemotherapy might diminish local, distant and circulating minimal residual disease. Yet, safety and feasibility of systemic chemotherapeutic treatments during pancreatic cancer resection have to be evaluated in a first instance.

Methods and analysis

This is a prospective, single-centre phase I/II feasibility study to investigate the safety and tolerability of a combination of intraoperative chemotherapy and surgical resection in pancreatic cancer. Forty patients with locally confined or borderline resectable pancreatic cancer, meeting all proposed criteria will be included. Participants will receive 400 mg/m^2 calcium folinate over 2 hours and 2000 mg/m^2 5-fluorouracil (5-FU) over 48 hours, started on the day before pancreatic surgery and thus continuing during surgery. Participants will be followed until 60 days after surgery. The primary endpoint is the 30-day overall complication rate according to the Clavien-Dindo classification. Secondary endpoints comprise toxicity and treatment associated complications. Patients receiving perioperative chemotherapy will be compared to a propensity score matched contemporary control group of 70 pancreatic cancer patients receiving the standard treatment. This trial also contains an ancillary translational study to analyse disseminated tumour cells and effects of pharmacologic interventions in pancreatic cancer.

Ethics and dissemination

Combicare has been approved by the German Federal Institute for Drugs and Medical Devices (reference number 4042787) and the Medical Ethics Committee of Heidelberg University (reference number AFmo-269/2018). The results of this trial will be presented at national and international conferences and published in peer-reviewed journals.

Trial registration number

DRKS00015766

Strengths and limitations of this study

- This is the first prospective clinical safety and feasibility study to evaluate a novel concept of systemic intraoperative chemotherapy during pancreatic cancer surgery.
- A strength of this study is the careful monitoring of any potential toxicity and treatment related complications, and the comparison of the safety profile of this multimodal therapy compared to the standard treatment by inclusion of a propensity score matched contemporary control group.
- If intraoperative chemotherapy during pancreatic cancer surgery proves to be safe, the data will be used as a baseline for a randomised controlled, phase III trial on the oncological effectiveness of this treatment.
- This study will provide valuable information for a better understanding of tumour cell dissemination and effects of pharmacological interventions in pancreatic cancer.

INTRODUCTION

Pancreatic cancer is the 4th leading cause of cancer-related deaths in the Western world, and it is one of only a few cancers for which mortality has increased since 1990[1]. In addition, mortality is projected to further increase, making this devastating disease the 2nd leading cause of cancer related death within the upcoming decade. With a 5-year survival rate of about 7%[2 3] the prognosis of pancreatic cancer is still very poor.

Surgical resection is the only curative treatment option and primary surgery followed by adjuvant chemotherapy is the current standard treatment for patients with resectable pancreatic cancer[4-7]. Local resectability of pancreatic cancer is determined by the involvement of adjacent major vessels and neighboring organs. An international consensus on the classification of resectability, especially of borderline resectable pancreatic cancer, has recently been developed by the International Study Group of Pancreatic Surgery (ISGPS)[8] and the International Association of Pancreatology[9]. However, only a minority of patients are diagnosed with resectable disease and even after potentially curative R0 resection the 5-year survival rate remains 15-30%[10-14]. The cornerstone of tumour resection in pancreatic cancer treatment has been further corroborated by a National Cancer Data Base study in the US, which showed that the 5-year survival rate of patients with resectable pancreatic cancer drops below 3% if surgery is omitted[13]. Following resection, adjuvant chemotherapy offers a survival benefit for pancreatic cancer patients, and numerous multicentre randomised trials performed over the past two decades showed considerable advances of chemotherapeutic regimens in the adjuvant setting[14-26]. Additional progress has been made in increasing the resection rate of locally advanced unresectable pancreatic

cancer by neoadjuvant chemotherapy, especially combinations of calcium folinate, 5-fluorouracil (5-FU), irinotecan and oxaliplatin (FOLFIRINOX)[27], associated with improved overall survival and potential cure. Neoadjuvant chemo(radio)therapy might also be beneficial in patients with resectable or borderline resectable pancreatic cancer[28-30].

Besides improvements in chemotherapeutic regimens, the safety of pancreatic surgery has considerably increased, with a reduction of postoperative mortality to 3%[12], which is mainly due to advances in complication management, especially at high-volume pancreatic surgery centres[12 31-33]. The most common and serious complication following pancreatic surgery is a leakage of pancreatic juice containing digestive enzymes out of the remnant pancreas, a so-called postoperative pancreatic fistula (POPF)[34 35]. The aggressive nature of the leaking pancreatic juice might cause life-threatening complications, including postpancreatectomy hemorrhage (PPH), or intraabdominal fluid-collection with superinfection leading to abscess formation and sepsis. These complications, together with delayed gastric emptying (DGE) and chyle leak following pancreatic surgery, have been comprehensively defined by the ISGPS with associated severity gradings[34-38]. Postoperative complications might delay adjuvant treatments or compromise their completeness, associated with diminished effectivity and increased risk of recurrent disease.

Despite advances in surgery and (neo-)adjuvant chemotherapy long-term survival of pancreatic cancer patients is still rare, due to frequent local or systemic recurrence[39-41], while the pathophysiology of recurrence remains largely unknown. Subclinical metastasis might occur early during tumour development[42 43], but iatrogenic tumor cell dissemination as a result of tumour manipulation during surgery is also a relevant concern[44 45]. There is evidence that cancer cells are continuously released from the primary tumour into the bloodstream and lymphatic system, and circulating tumour cells (CTCs) are further increased by standard pancreaticoduodenectomy[45]. Several studies have shown that high levels of CTCs are associated with tumor progression and poor prognosis in pancreatic cancer patients[46-48]. Since surgical manipulation of the tumour during pancreatic resection leads to dissemination of pancreatic cancer cells potentially founding the seeds for future metastases and local recurrence, perioperative systemic chemotherapy may reduce recurrence and thereby increase long-term survival by targeting intraoperatively shed cells as well as pre-existing micrometastases. Computational modeling of pancreatic cancer progression indicates that tumor cell growth inhibiting therapies earlier in the course of treatment are even more effective than upfront tumor resection[42]. So far, for pancreatic cancer no systemic intraoperative chemotherapeutic regimen has been studied in a standardized prospective manner to potentially reduce local and distant recurrences by targeting minimal residual

disease such as CTCs. There is limited evidence available demonstrating hyperthermic intraperitoneal chemotherapy (HIPEC) with gemcitabine after R0 pancreatic cancer resection leads to a survival benefit by controlling locoregional recurrence without increasing perioperative morbidity and mortality[49]. Cytoreductive surgery including multiorgan resection combined with HIPEC is a well-established treatment option for peritoneal carcinomatosis of several gastrointestinal tumour entities, and the operative risk of the procedure has been shown to be similar to any other major gastrointestinal surgery[50 51]. Likewise, perioperative chemotherapy including pancreatic and hepatic arterial infusion of 5-FU up to one week prior to pancreatic cancer resection and restarted again one week after surgery seemed to be safe and contribute to survival[52]. Therefore, intraoperative systemic chemotherapy during pancreatic resections should be well tolerated.

Thus, a multimodal treatment concept with a ***combi***nation of intraoperative ***C***hemotherapy ***a***nd surgical ***Re***section in patients with locally confined or borderline resectable pancreatic cancer (combiCaRe study) has been developed. Based on the above mentioned rationale it has been hypothesised that the number of CTCs can be reduced by this approach. This might translate into a longer interval from pancreatic cancer resection to tumour recurrence and extended overall survival. Because intraoperative chemotherapy for pancreatic cancer has not been tested in a standardized prospective trial, the feasibility and safety of this approach will be evaluated within this prospective, monocentric phase I/II study. In addition, translational aspects of tumour cell dissemination as well as effects of chemotherapy in pancreatic cancer tissue and blood will be determined. As a proof of concept the combiCaRe study aims to define the basis for a consecutive confirmatory phase III clinical trial investigating the oncologic benefit of this multimodal treatment.

METHODS AND ANALYSIS

Study design

The combiCaRe trial is a prospective, monocentric phase I/II clinical study, conducted at the high-volume pancreatic surgery centre of Heidelberg University Hospital (Germany) to determine the feasibilty and safety of a combination of intraoperative chemotherapy and surgical resection in locally confined or borderline resectable pancreatic cancer. This study was registered at the German Clinical Trials Register (DRKS00015766). The study protocol adheres to the SPIRIT recommendations (Standard Protocol Items: Recommendations for Interventional Trials)[53].

After screening for eligibility, written informed consent, and enrolment to the trial,

chemotherapy with 5-FU and calcium folinate will be started the day prior to surgery. Thereby adequate levels of cytotoxic substances will be reached within the systemic circulation during the critical period of tumour manipulation and potential intraoperative tumor cell dissemination. Pancreatic cancer surgery will be performed according to the standards of care in the Department of Surgery at Heidelberg University Hospital. Administration of chemotherapy will be continued for 48 hours in total. Postoperative care will be provided according to regular standards with particular attention to chemotherapy associated side effects. Adjuvant treatment regimens are performed according to current guidelines, starting up to 12 weeks after surgery. The study flow chart is presented in figure 1.

Study population and eligibility criteria

Patients with newly diagnosed resectable, or borderline resectable pancreatic cancer as defined by the ISGPS[8], located in the head of the pancreas, scheduled for elective primary pancreatic cancer resection will be approached for participation in this study. All patients will be informed in detail about the purpose of the trial, the surgical procedure, the perioperative chemotherapeutic treatment and potential benefits as well as risks. If the patient has given written informed consent to participate in the trial, inclusion and exclusion criteria (Box 1) will be carefully evaluated. Eligible patients will be enrolled into the trial. Screened patients who are not enrolled will be documented in the screening log, including the reasons for exclusion.

Box 1. Major inclusion and exclusion criteria of the trial

Inclusion criteria

- newly diagnosed, resectable or borderline resectable pancreatic cancer located in the head of the pancreas, without arterial involvement on cross sectional imaging (contrast enhanced CT scan) according to the International Study Group of Pancreatic Surgery (ISGPS) criteria[8]
- histologically or cytologically proven pancreatic ductal adenocarcinoma (including variants)
- ≥ 18 and ≤ 75 years of age
- capacity to consent
- written informed consent
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- patient considered to tolerate surgery and chemotherapy by a multidisciplinary team
- Women of childbearing potential and men must agree to use adequate contraception prior to study entry and for the duration of study participation. Childbearing potential is defined according to the “Recommendations related to contraception and

pregnancy testing in clinical trials“ of the Clinical Trial Facilitation Group (CTFG).

Exclusion criteria

- distant metastatic disease
- renal disease, creatinine clearance < 50 ml/min (estimated by Cockroft-Gault)
- abnormal hepatic function as defined by a total bilirubin level > 1.5 x the upper limit of normal (ULN), unless the patient has extrahepatic cholestasis due to pancreatic cancer, or alanine aminotransferase (ALT) > 2.5 x ULN, liver cirrhosis (of any Child-Pugh grade)
- serious cardiovascular disease (e.g. myocardial infarction in the last 12 months, congestive heart failure NYHA III/IV, unstable angina pectoris)
- severe chronic obstructive pulmonary disease (COPD), GOLD stage > II
- American Society of Anesthesiologists (ASA) score > III
- active infection, including cholangitis
- abnormal bone marrow function, defined as an absolute white blood cell count < 3/nl or platelet count < 100/nl
- pernicious anaemia or other megaloblastic anaemias where Vitamin B12 is deficient
- immunosuppressive therapy
- allergy or known intolerance to 5-fluorouracil (5-FU) or calcium folinate
- patients with a known lack of dihydropyrimidine-dehydrogenase (DPD)-activity or patients treated with DPD inhibitors such as brivudine
- current pregnancy or breastfeeding; each pregnancy that occurs within 6 months after the termination of the perioperative chemotherapy has to be reported
- history of another malignancy in the past 5 years
- inability to comply with the study and/or follow-up procedures
- (language) problems in understanding the patient information document explaining the present clinical trial
- concurrent participation in another clinical study
- any condition, which could result in an undue risk for the patient in the opinion of the investigator

Subject withdrawal

Subjects may withdraw their consent at any time, without stating the reason and without any disadvantage. Patients may also be excluded for other reasons, if the investigator assesses a continuation of the treatment as detrimental to the subject's well-being.

Sample size

This exploratory study focuses on the feasibility and safety of the therapeutic interventions. No formal sample size calculation has been performed. Therefore, we have chosen a number of patients, which is estimated to be sufficient to obtain first data on feasibility and safety of the intervention. Forty patients are planned to be enrolled in this trial, including 5 patients who potentially drop out intraoperatively, e.g. due to liver or peritoneal metastasis revealed by exploratory laparotomy. To compare the outcomes of the intervention group with a similar control group, the enrolled patients will be matched by propensity score with a contemporary cohort (age, procedures, histopathological findings, and medical history) extracted from the pancreatic surgery databases of the Department of Surgery at Heidelberg University Hospital in a 1:2 ratio. This sample size (35:70) would be large enough to detect a standardized mean difference (Cohen's d) of about 0.6 with 80% power and a significance level of 5%. A subsequent randomised controlled trial is planned with further sample size calculation based on the results of this trial and all other available data.

Study procedures

Perioperative chemotherapy

Chemotherapy with 5-FU is started 12-18 hours prior to surgery and continued until postoperative day 1. Thereby adequate systemic levels of cytotoxic substances will be reached during the critical period of tumour manipulation and potential intraoperative tumour cell dissemination. Overall, 1000 mg/m^2 5-FU per day are applied for 48 hours (total dose 2000 mg/m^2). The 5-FU infusion is administered via peripheral vein catheter. Immediately prior to 5-FU, 400 mg/m^2 calcium folinate will be given intravenously over 2 hours.

Surgery, biospecimen and data collection

(Partial) pancreaticoduodenectomy will be performed according to the standards of care in the Department of Surgery at Heidelberg University Hospital. Peripheral blood will be collected prior to the start of chemotherapy, as well as on postoperative days 3, 7, 14 (or day of discharge) and 30. Intraoperatively, peripheral and portal venous blood, bone marrow and tumour tissue dispensable for pathological diagnosis and staging will be collected for translational studies. The department's well-established and highly standardized local biobanks will be the backbone of this study. Perioperative management and postoperative care will be provided according to regular standards with particular attention to chemotherapy-associated side effects. In addition, on postoperative days 3, 7, 14 (or the day

of discharge) qualified study personnel will visit the patient for the assessment of the study endpoints and to take peripheral blood. Thirty days after surgery patients will be examined in the department's outpatient clinic for the occurrence of any further surgery- or chemotherapy-related complications. Sixty days after surgery patients will be contacted by telephone and asked for the occurrence of any further intervention-related complications. Adjuvant treatment regimens are performed according to current guidelines and in accordance with the recommendations of the National Centre of Tumour Disease (NCT) of Heidelberg University Hospital, starting up to 12 weeks after surgery. Patients are followed until postoperative day 60.

Study endpoints

Primary study endpoint

The primary objective of this study is to determine the safety of a perioperative chemotherapeutic regimen in combination with pancreatic cancer resection, which will be measured by the overall 30-day complication rate according to the Clavien-Dindo classification[54]. In parallel, the feasibility of this novel treatment concept will be assessed by the completeness of perioperative chemotherapy administration in relation to its toxicity, timely patient recruitment, and proper collection of biospecimen.

Secondary study endpoints

Key secondary outcomes include:

- 60-day complication rate according to the Clavien-Dindo classification[54]
- 30- and 60-day mortality
- pancreas-associated postoperative morbidity: POPF, PPH, DGE, and chyle leak (according to the ISGPS definitions[34-38]), intraabdominal fluid-collection or abscess
- bile leakage, including insufficiency of the biliodigestive anastomosis
- perioperative bleeding
- gastrointestinal bleeding
- postoperative ileus
- duration of intensive care unit (ICU) stay (postoperative and readmissions)
- postoperative duration of hospital stay
- need for readmission
- anaemia (Hb < 8 g/dl), thrombocytopenia, leukopenia
- postoperative sepsis
- allergic reactions

- serotonin syndrome
- mucositis (stomatitis, cheilitis, esophagitis, proctitis), diarrhea, nausea, vomiting
- alopecia, hand-and-foot syndrome
- central neurotoxicity, peripheral neuropathy
- renal failure (serum creatinine, BUN, urine production)
- liver damage (AST > 5 x ULN, ALT > 5 x ULN, AP > 5 x ULN, GGT, bilirubin > 1.5 x ULN)
- cardiotoxicity
- bronchospasm
- perioperative tumour cell dissemination (circulating tumor cells, CTCs)
- pharmacokinetics of perioperative chemotherapy

Safety objectives and assessment of safety

The incidence of all adverse events (AEs) will be closely monitored and evaluated. Hereby, only events that occur after the study inclusion and during the follow-up period will be collected. All AEs and intervention related side effects will be documented on the specific forms and will be reported regardless of causality. In addition, each serious adverse event (SAE) has to be documented on a SAE form and transmitted to the pharmacovigilance department within 24 hours after investigator's awareness of its occurrence. Following treatment of the first 10 patients recruitment will be interrupted for at least 30 days until an interim analysis for safety has been performed. If one of the following specific stopping criteria will be reached, the combiCaRe trial will be stopped immediately: grade B or C POPF[34 35] in more than 5 patients; insufficiency of the biliodigestive anastomosis in more than 4 patients; death within 30 days in more than 2 patients.

Ancillary translational study

CTCs will be quantified, molecularly and functionally analysed in the systemic circulation and portal venous blood before, during and after pancreatic cancer resection. In addition, disseminated tumor cells (DTCs) in the bone marrow will be assessed via bone marrow biopsy during surgery. The effects of perioperative chemotherapy on CTC and DTC biology will be determined. The biodistribution of 5-FU within pancreatic cancer tissue following perioperative 5-FU administration and oncologic resection will be analysed and potential immediate effects of pharmacologic interventions on tumour cell survival will be monitored in resected pancreatic cancer tissue. Comprehensive histopathological and molecular analyses will be performed for in depths characterisation of immediate immune responses to

chemotherapy-induced cell death in pancreatic cancer. Further functional assays using organ culture systems will help to determine the effect of 5-FU treatment on stroma - tumor cell crosstalk within an intact tumour microenvironment, and provide a valuable *in vitro* tool for screening drugs with potential synergistic antitumour activity. This might help to design more efficient, personalised (immuno)therapies against pancreatic cancer.

Data handling and monitoring

All protocol-required information collected during the trial must be entered by the investigator, or designated representative, into the electronic case report form (eCRF). The completed eCRF must be reviewed and authorised electronically by the investigator or by a designated co-investigator. To guarantee high data quality, data validation rules will be defined in a data validation plan. Completeness, validity and plausibility of data will be checked using validating programs, which will generate queries. A tracking system for eCRF data and queries will be established to guarantee that data is managed in a timely manner. All data management procedures will be conducted according to written defined standard operating procedures (SOPs) of the Institute of Medical Biometry and Informatics (IMBI) at Heidelberg University Hospital that guarantee an efficient conduct complying with Good Clinical Practice (GCP). To ensure confidentiality of patients' personal information data will be stored, and analysed in a pseudonymised manner and protected against unauthorised access. Only participating investigators or designated representatives will have the authority to access the data. Monitoring will be conducted by the Coordination Centre for Clinical Trials (KKS) Heidelberg. The monitor ensures that the trial is conducted according to study protocol and regulatory requirements by review of source documents, entries into the eCRF and essential documents.

Statistical analysis

The empirical distribution of all endpoints will be calculated, including mean, standard deviation and quartiles in case of continuous variables and scores, and with absolute and relative frequencies in case of categorical data. Two-sided 95% confidence intervals will be calculated. Descriptive p-values of the corresponding statistical tests comparing the two samples (intraoperative chemotherapy and surgical resection vs. surgical resection alone from historical control) will be reported. Whenever appropriate, statistical graphics will be used to visualize the findings. Besides an intention-to-treat (ITT) analysis, a modified ITT analysis will be performed to separately analyse patients receiving partial pancreaticoduodenectomy including a pancreatico-digestive anastomosis.

Ethics

The trial will be carried out in conformity with the "Ethical principles for medical research involving human subjects" of the 18th World Medical Association General Assembly in Helsinki (1964), including all amendments. The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) harmonised tripartite guideline on Good Clinical Practice (ICH-GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements. The protocol of the combiCaRe trial (version 02, date July 27th 2018) was approved by the German Federal Institute for Drugs and Medical Devices (reference number 4042787) on August 20th 2018 and reviewed by the Medical Ethics Committee of Heidelberg University that provided a favourable opinion (reference number AFmo-269/2018) on September 11th 2018. Thus, all measures have been taken to guarantee patient welfare and minimise ethical concerns. Any subsequent protocol amendments must be evaluated by the ethics committee and competent authority.

As described above, systemic chemotherapy during HIPEC is an established treatment regimen in colorectal cancer or other malignancies spread to the peritoneal cavity. 5-FU based regimens have been shown to be effective in (neo)adjuvant and palliative pancreatic cancer therapy. Therefore, the perioperative application of 5-FU can be performed during a standard pancreatic cancer resection without expected SAEs. General complications of both, the chemotherapeutic regimen and surgical procedures, are subject of patients' informed and written consent. The occurrence of all treatment-emergent adverse events (TEAEs), AEs, SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be rigorously monitored. Immediate intervention or treatment is available in case of an acute AE.

Before being enrolled in the study, the subject is informed about the nature, scope and possible consequences of the study in a way understandable to the patient. An informed consent document that includes both information about the study (including ancillary translational study) and the consent form is prepared and given to the subject in a language understandable to the patient. After reading the informed consent document, the subject must give written informed consent to participate in the study. A copy of the signed consent document is given to the subject and the original document is retained by the investigator. Without the patient's written informed consent, any measures or procedures required only for

the clinical study are not permitted.

Patient and public involvement

Although patients or public were not involved in the design of the present study, our first priority was the patients' well-being. Patients will be informed about novel insights with regard to this clinical trial that might be relevant to their participation in this study. At any time, participants can be informed about study outcomes through the principal investigator. Furthermore, the results of this study are planned be presented at meetings of self-supporting groups for patients with pancreatic diseases and their relatives and friends, e.g. the "Arbeitskreis der Pankreatektomierten e.V.".

Dissemination

The results of this trial will be presented at relevant national and international conferences and will be published in peer-reviewed journals, regardless of the outcome of this study. After analysis of the primary endpoint a first manuscript reporting study results is planned to be published as soon as possible. All presentations and manuscripts will be reviewed by the principal investigator to prevent forfeiture of patient rights to data not in the public domain.

Author contributions

S.R., C.S., M.K.D., C.W.M. and T.H. designed the study protocol. C.T., P.K., U.K. and M.M. contributed to the study design. D.J., M.W.B and T.H. initiated this clinical study. S.R. and T.H. wrote the paper. All authors approved the final manuscript.

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Disclaimer

The sponsor and funders have no role in the study design, data collection and analysis, nor in publication of study results.

Competing interests statement

None declared.

Trial status

Recruitment planned.

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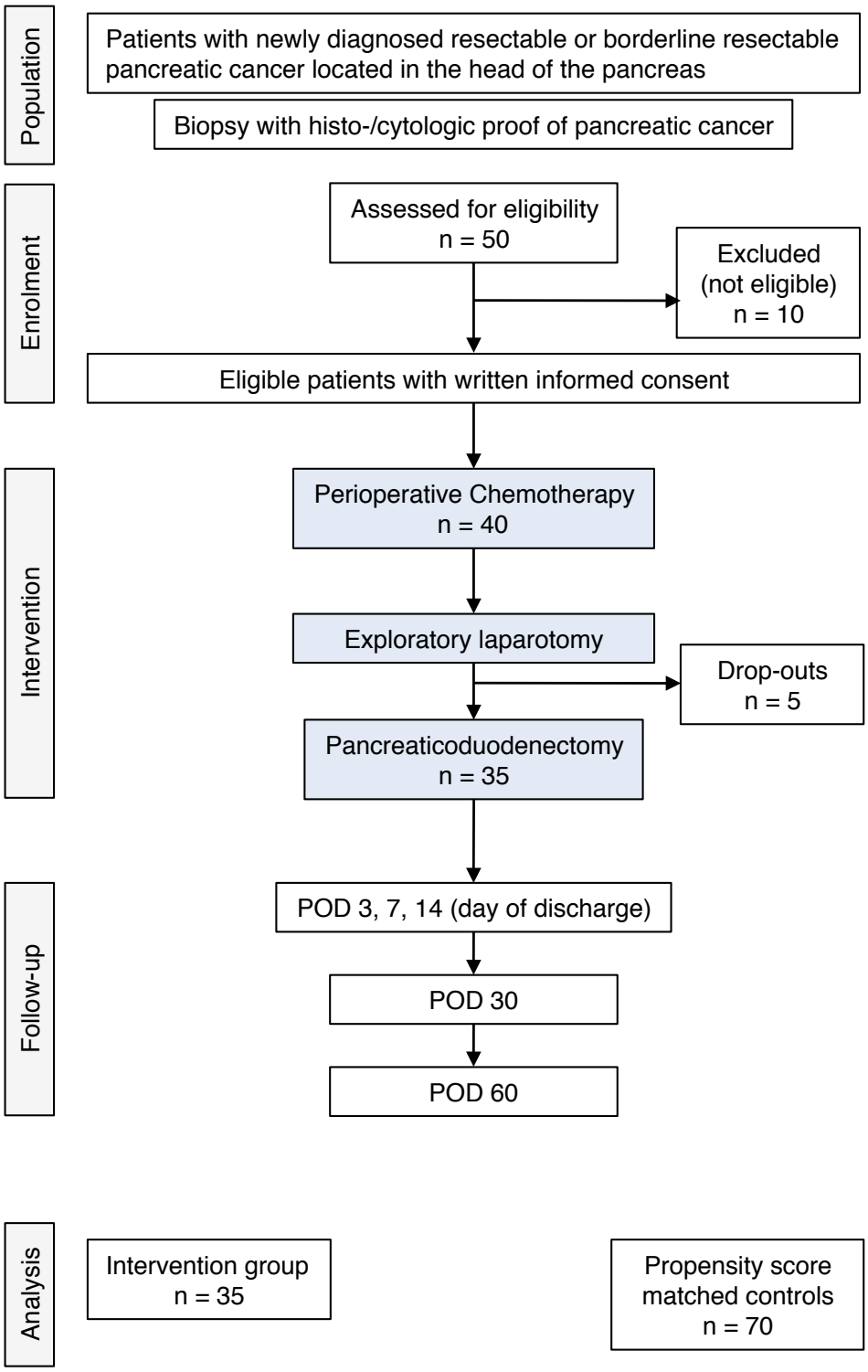
FIGURE LEGENDS

Figure 1. Study flow chart. CTx: Chemotherapy with 5-fluorouracil (5-FU) and calcium folinate; pod: postoperative day.


Population
Patients with newly diagnosed resectable or borderline resectable pancreatic cancer located in the head of the pancreas
Biopsy with histo-/cytologic proof of pancreatic cancer
Enrolment
Assessed for eligibility n = 50
Excluded (not eligible) n = 10
Eligible patients with written informed consent
Intervention
Perioperative Chemotherapy n = 40
Exploratory laparotomy
Drop-outs n = 5
Pancreaticoduodenectomy n = 35
Follow-up
POD 3, 7, 14 (day of discharge)
POD 30
POD 60
Analysis
Intervention group n = 35
Propensity score matched controls n = 70

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/ item	Item No	Description	Manuscript page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**2**
	2b	All items from the World Health Organization Trial Registration Data Set	**see DRKS registry**
Protocol version	3	Date and version identifier	**12**
Funding	4	Sources and types of financial, material, and other support	**14**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**1, 14**
	5b	Name and contact information for the trial sponsor	**14**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**14**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**Not applicable**
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**3-5**
	6b	Explanation for choice of comparators	**8**
Objectives	7	Specific objectives or hypotheses	**9-10**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**5-6**
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**5**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**6-7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**8**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**7, 10**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**Not applicable**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**Not applicable**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**9-10**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**Figure 1**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**8**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**Not applicable**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**Not applicable**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**Not applicable**

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**Not applicable**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**Not applicable**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**Not applicable**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**8-9**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**Not applicable**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**11**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**11-12**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**11-12**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**11-12**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**11**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**10**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**10**

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**Not applicable**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**12**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**12**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**12-13**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**12-13**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**11**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**14**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**11**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**Not applicable**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**13**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**Not applicable**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**Not applicable**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**Available at request**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**Available at request**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.